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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,865	02/11/2000	PHILIP JOHN BURKE	ERD100	1461

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	25

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,865	BURKE ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,31-33 and 40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31-33,40 and 42-44* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

The Amendment filed March 3, 2003 (Paper No. 24) in response to the Office Action of December 3, 2002 is acknowledged and has been entered.

Claims 42-44 were added.

Claims 29, 31-33, and 40-44 are pending and are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Objections Maintained:

Claim 41 remains objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 31-33, 40, and 42-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29 and 42 include the limitation of "**substituted** alkyl" including "substitution by CONH2, OH, halogen, CN and COOH" or "substituted aryl", etc.. In the absence of the identity of moieties which are intended to be substituted, thus modifying an art recognized chemical core, described structurally or by chemical name, the identity of "substituted" would be difficult to ascertain. In the absence of said moieties, the claims containing the term "substituted" are not described sufficiently to distinctly point out that which applicant intends as their invention. See claim 44 for correct format.

Claims 29, 31-33, 40, and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedlos *et al.* (Biochem. Pharmacol. 44(9) pages 1739-43, 1992, IDS.. **hereinafter Friedlos#1**) and Friedlos *et al.* (Biochem. Pharmacol. 44(1), pages 25-31, 1992, IDS..**hereinafter Friedlos#2)** in view of Jaiswal, A. (J.Biol.Chem. 269(20), pages 14502-08, 1994, IDS).

1. Friedlos#1 and Jaiswal, A. (J.Biol.Chem. 269(20), pages 14502-08, 1994, IDS) teach as set forth in Paper No. 23, pages 4-6.
2. Friedlos#1 do not specifically identify other reduced pyridinium derivatives that are equivalent to the co-factors NRH or NADH in the reduction of CB 1954 by DT diaphorase.

3. Friedlos#2 teach the identification of novel reduced pyridinium derivatives as synthetic co-factors in the reduction of CB 1954 by the enzyme DT Diaphorase (page 28, 1st column, last paragraph, and Table 1). Specifically, Friedlos#2 teach (page 28, 2nd column) that the actual structural requirements in a co-factor of DT diaphorase are fairly lax and, indeed, it would appear that there is little requirement for the adenine nucleotide portion of NAD(P)H at all. Thus, the simplest quaternary (and therefore reducible) derivative of nicotinamide, 1-methylnicotinamide, was as good a co-factor as NAD(P)H.

Newly amended claim 29, and new Claims 42-44, drawn to an analogue of NRH, encompass 1-methylnicotinamide: With regards to Claim 29, R1 is an alkyl, R2 and R3 are independently H, and R4 is H. With regards to Claim 42, R is an alkyl, wherein the alkyl group is C_1 (Claim 43), and or wherein R is $-CH_3$ (Claim 44).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the method of Friedlos#1 so as to administer to a human patient with cancer the prodrug CB1954 and nicotinamide riboside (reduced) (NRH) or an analogue thereof. One would have been motivated to do so because Friedlos#1 teach that the lack of success of CB 1954 as an anti-tumor agent in humans is because of the relative inactivity of human DT diaphorase (NQO1) towards CB1954, however such inactivity *can be overcome* by the addition of reduced pyridinium co-factors (i.e. NADH or NRH) resulting in enhanced cytotoxicty of CB1954. **Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute NRH (or NADH)**

employed by Friedlos#1 with an equivalent analogue of NRH such as 1-Methylnicotinamide because Friedlos#2 teach that the simplest quaternary (and therefore reducible) derivative of nicotinamide is 1-methylnicotinamide, which was as good a co-factor as NAD(P)H.

Thus, since it is well known in the art that CB-1954 is a potent anti-tumor agent in-vivo capable of curing the rate Walker 256 carcinoma via the activity of NQO1 converting the drug to a cytotoxic form, one would have a reasonable expectation that the pro-drug and 1-methylnicotinamide would also be converted into a cytotoxic form in a human patient since Friedlos#1 have shown that the relative inactivity of human DT diaphorase (NQO1) towards CB1954 *can be overcome* by the addition of NADH or NRH in human tumor cells in-vitro and that 1-methylnicotinamide is an equivalent co-factor (Friedlos#2). Further, although Friedlos#1 does not characterize the target cells as expressing NQO2, any administration of the claimed compounds would anticipate target cells to be destroyed as expressing NQO2 since it was well known in the art at the time the invention was made that NQO2 was expressed in several human tissues including heart, lung, liver, skeletal muscle, kidney, and pancreas (See teachings of Jaisawl, Paper No. 23, page 5). Moreover, since Jaisawl teaches that the protein encoded by the NQO2 gene catalyzes 4-nitroreduction of the anti-tumor compound CB10-200 with almost "equal efficiency" as the NQO1 protein, and since CB10-200 **and CB1954** are nitrophenylaziridine analogs, i.e. members of the same family of anti-tumor agents, it would have been obvious to one of ordinary skill to determine whether or not such target cells expressed NQO2 (or NQO1) prior to the administration of the prodrug and NRH or an analogue thereof such as 1-methylnicotinamide because such a determination would obviously enhance the efficacy of the treatment. In other words, if the target cells did not express NQO2 or NQO1,

it would be obvious to one of skill in the art that such an administration would not effectively destroy the target cell.

Applicants argue (Paper No. 24, page 5), that independently, neither Friedlos#1 nor Jaiswal teach an analogue of NRH as newly claimed. However, in view of the newly amended claims, and in view of the teachings of Friedlos#2, applicants' arguments are not found persuasive.

No claim is allowed.

All other rejections and or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol Ph.D.
Examiner
Art Unit 1642

GN
May 13, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600